Interim guidelines for the follow-up of ASCUS Pap smears have recently been published. Future trends in the use of the system should include increased consistency in using the ASCUS diagnosis and a better understanding of the diagnostic problem this term is trying to communicate, so that appropriate follow-up can be instituted.

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Serum Prostate-Specific Antigen Assay—An Update

PROSTATE-SPECIFIC ANTIGEN (PSA) is synthesized in the epithelial cells of the prostate gland and is perhaps the best tumor marker discovered thus far. The tissue specificity of PSA makes it the most useful marker available for the diagnosis and management of prostate cancer. Lack of cancer specificity is its only drawback. Benign conditions, such as benign prostatic hyperplasia, prostatitis, and infarction, can also be associated with elevated serum PSA levels. Because prostate cancer is frequently associated with old age in men and is a major cause of death for men, a test capable of detecting prostate cancer before the lesion extends outside the confines of the prostate gland is in demand.

Clinical Utility

Because of its tissue specificity, the PSA assay is particularly useful for monitoring the success of surgical prostatectomy. Complete removal of the prostate should result in an undetectable PSA level; any measurable PSA after radical prostatectomy would indicate residual prostatic tissue or metastasis. In those cases, increasing PSA concentrations strongly indicate a recurrent disease. If, however, the detectable serum PSA level after radical prostatectomy is caused by incomplete resection of the gland and not persistent disease, the level should remain unchanged on extended follow-up. Because of the specificity of PSA, the ability of the assay to detect residual prostatic tissue or the recurrence of prostate cancer at an early stage cannot be replicated by other tumor markers. It should be noted that the half-life of serum PSA is about 3 to 4 days; therefore, it will take 30 days for a serum PSA at 50 μg per liter (50 ng per ml) to drop to an undetectable range after surgical therapy. Measuring the PSA level within a month after curative radical prostatectomy is not recommended. Also, serum PSA should not be measured during the course of irradiation treatment, as a transient and modest increase of PSA may occur that could be misinterpreted as disease progression.

The tissue specificity of PSA also makes the test an excellent tool for detecting recurrence after radical prostatectomy. There has been a great demand for the development of an ultrasensitive PSA test that would allow recurrence and metastasis to be detected early, thus providing a better opportunity for successful treatment. Many commercial PSA tests now available are capable of detecting serum PSA levels below 0.1 μg per liter.

In general, no tumor markers are recommended for screening. The use of serum PSA levels in combination with either digital rectal examination (DRE) or transrectal ultrasonography of the prostate as a screening tool for detecting clinically important prostate cancer has been recommended by some. Screening may not only prevent the death of about 30,000 to 40,000 active men from prostate cancer each year, but also permit treatment of organ-confined, potentially curable prostate cancer discovered in men with a life expectancy of more than ten years.

Improvements on Assay Use

The PSA test is tissue- but not cancer-specific. There is substantial overlap in serum PSA levels between men with benign prostatic hyperplasia and those with prostate cancer, especially in the range of 4 to 10 μg per liter. Therefore, there is also a need to improve the current PSA test to differentiate between the two disorders. Two interesting and noteworthy new approaches have been developed for improving the specificity and sensitivity of PSA testing: the measurement of PSA density and the determination of the rate of increase in PSA concentration.

One approach has been to divide the serum PSA concentration by the volume of the prostate gland (determined by transrectal ultrasonogram); the result is the PSA density. A mildly elevated serum PSA level associated with a small prostate gland may be indicative of cancer, whereas the same value in a patient with a large gland may be indicative only of benign hyperplasia. It was recommended that if the findings of the DRE are normal and the serum PSA level is between 4 and 10 μg per liter (by Hybritech assay), the patient should undergo transrectal ultrasonography to determine the volume of the prostate gland. The mean PSA density has been established as 0.285 for men with positive biopsy results and 0.199 for men with negative biopsy results. The merit of PSA density is to distinguish benign prostatic hyperplasia from prostate cancer for men who have serum PSA levels within the intermediate range (4 to 10 μg per liter) who have had normal findings on a DRE, but it may not detect all organ-confined prostate cancers.

Another approach to improve the specificity of the serum PSA test is to calculate the rate of change of serum PSA levels. This rate appears to be more useful than the actual serum PSA level for detecting and staging prostate cancer. For example, for serum PSA values well within the reference range (< 4 μg per liter), a change from 1.8 to 2.9 μg per liter in a year's time could signal the presence of prostate cancer. If the PSA test selected is reliable over that period of time, this new approach allows for the early detection of cancers at a more curable stage than would have been possible with conventional criteria. It is now recommended that PSA velocity should be determined from three consecutive measurements within a year. A PSA velocity test showing a consistent increase of 0.75 μg per liter per year or greater, based on three consecutive determinations, is suggestive of cancer and warrants further evaluation. Both new approaches point out that PSA concentrations can be in the normal range even in the presence of cancer. Consequently, an accurate and precise determination of PSA levels within the normal concentration range will be required to take advantage of these two new methods.

One area that has not received enough attention is the use of age-adjusted reference values, especially the normal reference range for people at an older age. An age-specific reference range for serum PSA would possibly detect organ-confined prostate cancers earlier in younger men (men with a life expectancy longer than 10 years) at a time when the tumors are possibly more susceptible to cure. Based on the new reference ranges, fewer cancers in older men—who might have clinically insignificant tumors or have a less than ten years' life expectancy and not benefit from surgical treatment—will be detected. In the past, 4 μg per liter was the upper normal cut off for men at all ages. The recommended age-specific serum PSA reference ranges are 0.0 to 2.5 μg per liter for men 40 to 49 years, 0.0 to 3.5 μg per liter for men 50 to 59 years, 0.0 to 4.5 μg per liter for men 60 to 69 years, and 0.0 to 6.5 μg per liter for men 70 to 79 years. Studies have indicated that the new age-specific serum PSA reference ranges appear to make PSA a more sensitive tumor marker for men younger than 60 years and a more specific tumor marker for men older than 60 years.

Prostate-Specific Antigen Composition in Serum

Prostate-specific antigen has recently been found to be a serine protease capable of complexing with various protease inhibitors. Consequently, PSA is not free in the blood circulation, but exists largely as PSA complexes with protease inhibitors. The major form of PSA complexes found in the serum is PSA–α_1-antichymotrypsin. The ratio between PSA–α_1-antichymotrypsin and free PSA in the serum is not constant; the ratio increases with increasing concentrations of total PSA. Most important is the finding that the percentage of PSA–α_1-antichymotrypsin complex of the total serum PSA is higher in patients with prostatic cancer than in those with benign prostatic hyperplasia. Therefore, the PSA–α_1-antichymotrypsin value has a higher sensitivity for cancer than the assay for total PSA. In other words, the free serum levels of PSA are substantially lower in patients with untreated prostate cancer than in those with benign hyperplasia; the free serum PSA concentration does not correlate with the total serum PSA or PSA–α_1-antichymotrypsin.

Unfortunately, all current PSA kits were designed to measure free PSA in the serum. Also, PSA values produced by different commercial kits are not always compatible. There are two major reasons for these discrepancies: antibodies used in various commercial PSA kits do not have the same specificities for both free PSA and PSA–α_1-antichymotrypsin complex in the serum, and the calibrators used in various kits not only are not identical to each other, but also do not match the PSA composition found in patients' serum. It was suggested from many studies that the lack of a uniform calibrator among various commercial kits largely accounts for the different PSA values produced by different kits on the same specimens.

New-Generation Assay

A logical improvement for the current PSA kits is to change the focus from the measurement of total PSA to that of PSA–α_1-antichymotrypsin complex, because there is an excellent correlation between serum concentrations of PSA–α_1-antichymotrypsin and total PSA in random and in serial specimens. Therefore, using an assay that specifically measures the PSA–α_1-antichymotrypsin complex in the serum not only simplifies the preparation of a calibrator, but eliminates the difficulty of antibody selection. The new-generation assay, which will be available soon, will also improve the test's specificity for prostate cancer.

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Specimen Quality and Accuracy of Fine-Needle Aspiration Biopsies

OVER THE PAST 20 years, fine-needle aspiration biopsy (FNAB) has become an increasingly popular tool in the United States for diagnosing palpable and—with the adjunctive use of computed tomography (CT) or ultrasonography—deep-seated lesions arising in many body sites.

The accuracy of fine-needle aspiration as an effective diagnostic tool has varied greatly in recent reports: the sensitivity of FNAB to detect malignant neoplasms has ranged from 65% to 98% and the specificity (the ability to rule out malignant neoplasms unequivocally) from 34% to 100%. Looking at these results, the questions are why there is such a vast discrepancy and whether the test has use. In well-trained, experienced hands, however, FNAB is an accurate, cost-effective, and well-tolerated diagnostic procedure.